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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,291	06/10/2005	Kazufumi Yazaki	Q88235	9414

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EXAMINER	
MEAH, MOHAMMAD Y	
ART UNIT	**PAPER NUMBER**
1652	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,291	YAZAKI ET AL.	
	Examiner	Art Unit	
	Mohammad Meah	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *1-3 and 17-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/10/05, 12/28/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-19 are pending in the instant application for examination. With preliminary amendment of 10/23/06 applicant elected without traverse group II (claims 4-16) for examination.

Election/Restriction

During the preliminary amendment of this application, the applicant, on date 10/23/2006 elected without traverse Group II (claims 4-16), drawn to a mutant strain of *E. Coli*, for examination. Groups I and III-V (claims 1-3 and 17-19) are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to as non-elected groups.

Priority

Acknowledgement is made of applicant's priority date based on PCT application filing date of 12/11/2003 for PCT/ JP03/15882 and filing date 12/12/2002 for foreign application Japan 2002-360564.

Claim Rejections

35 U.S.C 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4-16 - the recitation "highly " is confusing and vague.as it is uncertain how much high or what amount by "highly" it refers.

Claim 6, line 2- "wherein an exogenous-- " should be "wherein the exogenous--" and the recitation in line 3- " mutation of a plasmid--" and –" into an *Escherichia coli* –" should be " mutation of the plasmid--" and –" into the *Escherichia coli-".*

Claim 8, line 3- "mutation of a plasmid -- " should be "-mutation of the plasmid --"

Claim 9, line 2- "an ammonia lyase-- " should be "- the ammonia lyase-- --"

Claim 15 - the recitation " derivative strain---from *Escherichia coli* SD 840-- " is confusing and vague as it is unclear whether the said derived *Escherichia coli* strain is obtained from *Escherichia coli* SD 840 or from any other *Escherichia coli* strain.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of *E. coli* strain having high expression of any exogenous gene or a genus of *E. coli* strain having high expression of phenylalanine ammonia lyase selected using stress response index. The *E. coli* strain claimed in the instant claims, having high expression of any exogenous gene or a genus of *E. coli* strain having high expression of phenylalanine ammonia lyase selected using stress response index by any means, is a large variable genus *E. coli* strains expressing many exogenous proteins. The specification teaches a few *E. coli strains* having high expression of an exogenous gene encoding a phenylalanine ammonia lyase selected using stress response index (*E. coli* SD840 page 12 of the specification), which does not represent all strains recited in the instant claims. The specification neither teaches the structures of all genes nor teaches how all *E. coli* strains will be modified. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed. Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 4-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a few *E. coli* strains (*E. coli* SD840 of page 12 of the specification) does not reasonably provide enablement for any *E. coli* strain having high expression of any exogenous gene or a genus of *E. coli* strain having high expression of phenylalanine ammonia lyase selected using stress response index. The claims broadly recite high expression of any *E. coli* strain using any exogenous gene or a genus of *E. coli* strain having high expression of phenylalanine ammonia lyase selected using stress response index. The specification fails to describe how any *E. coli* strain be modified to express any exogenous gene or any phenylalanine ammonia lyase gene.

Claims 4-13 are so broad as to include many strains of *E. coli* having high expression of any exogenous gene or any phenylalanine ammonia lyase selected using stress response index by any means. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number *E. coli* strains expressed with any gene. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the

proteins' structure relates to its function. However, in this case the disclosure is limited to a few genes such as specific phenylalanine ammonia lyases.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable(e.g., see Ngo et al. in the protein folding problem and tertiary structure prediction, 1994, Merz et al. (ed.), Birkhhauser, Boston, MAS, pp 433 and 492-495). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. Furthermore, there are many means of controlling gene function such as mutations of the gene itself, addition of inhibitors, modification of endogenous modulators, mutating individual nucleic acid, etc. It is not routine in the art to control a gene by any means to obtain desired outcome. Without knowing the structural feature of the protein it encodes, controlling the gene by any means (i.e., such as modification of the gene by mutations) to obtain desired function is unpredictable (e.g., see Ngo et al. in the protein folding problem and tertiary structure prediction, 1994, Merz et al. (ed.), Birkhhauser, Boston, MAS, pp 433 and 492-495). Enough guidance is not given to enable the skilled artisan to express any *E coli* strain with a large number of genes and select highly expressed strains using stress response. The specification does not

support the broad scope of the claims which encompass any *E. coli* strain expressed by any gene and how *E coli* strains' stress response regulated by by any means with any gene encoding any protein because the specification does **not** establish: (A) regions of the DNA structure of a gene which should be modified to control expression and/or to regulalte any *E. coli* strain's stress response (B) the general tolerance of *E. coli* stress response and expression in the modification of gene and extent of such tolerance towards the expression of the gene; (C) a rational and predictable scheme for modifying any gene residues with an expectation of obtaining the desired biological function; and / or controlling the gene by any means towards such biological function (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any *E. coli* strain having high expression of any exogenous gene selected using stress response index. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, selecting any *E. coli* strain expressed with any exogenous gene is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

CLAIM Rejection - 35 U.S.C 102

35 U.S.C 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 4, 6 rejected under 35 U.S.C. 102(b) as being anticipated by Hitagawa et al. (JP 08-140671).

Hitagawa et al. teach a mutant *E. coli* strain that expresses an exogenous gene wherein said mutant strain has high stress response (high heat shock transcription index or factor) and can maintain an unstable protein, such as an extraneous protein stably expressed in cell bodies.

CLAIM Rejection - 35 U.S.C 103a

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 4-15 are rejected under 35 U.S.C. 103(a) by Lockwood et al (WO 94/19472) and in view of Rowbury et al. (J. appld. Microbiol. 2001, 90, 677-695) and Seaver et al. (J. Bacterol. 2001. pp 7182-7189).

Claims 4-15 are directed to *E. coli.* strain which express exogenous gene encoding pal protein wherein said strain has high stress response factor and wherein said strain is selected by measuring hydrogen peroxide decomposition activity as a stress response factor.

Lockwood et al (WO 94/19472, in IDS) teach an *E. coli.* strain that highly expresses genes encoding unstable proteins, such as the Pal protein. However Lockwood et al (WO 94/19472) is silent about a correlation between stress response and high an expression of exogenous gene in *E. coli.*

Rowbury et al. (J. appld Microbiol 2001, 90, 677-695) teach that for cells of microorganisms, such as *E. coli* the stress response increases upon high expression of exogenous genes.

It would have been obvious to a person of ordinary skill in the art to correlate high expression in *E. coli*. strain of the exogenous gene (encoding the unstable protein Pal) with the stress response as taught by Rowbury et al.

Seaver et al. teach measurement of hydrogen peroxide decomposition activity in growing *E. coli* as a means of stress response factor.

It is easier to monitor high expression of an exogenous gene in *E. coli* by measuring the stress response factor hydrogen peroxide.

Therefore a person of ordinary skill in the art is motivated to use Seaver's method of measuring hydrogen peroxide decomposition activity to select **high stress response *E. coli strain*** wherein **increase of exogenous gene** is correlated with increase in **stress response** of said *E. coli* strain as taught by Rowbury et al.

As such it would have been obvious to one of ordinary skill in the art to express an *E. coli* strain with an exogenous gene encoding unstable proteins such as Pal as taught by Lockwood et al (WO 94/19472) and then use the Seaver's method of measuring hydrogen peroxide decomposition activity to select **high stress response** *E. coli* strain. The expectation of success is high that the selected **high stress response** *E. coli* strains highly express genes encoding unstable proteins, such as the Pal since increase of expression of exogenous gene is correlated with increase in stress

response of *E. coli* strain (Rowbury et al.). Therefore claims 4-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lockwood et al (WO 94/19472) in view of Rowbury et al. (J. appld. Microbiol. 2001, 90, 677-695) and Seaver et al. (J. Bacterol. 2001. pp 7182-7189).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you

have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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